IPASS: A Study on the Tolerability and Effectiveness of Injectable Testosterone Undecanoate for the Treatment of Male Hypogonadism in a Worldwide Sample of 1,438 Men

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ABSTRACT

Introduction. Morbidity/mortality is higher in men with below-normal serum testosterone. Restoring testosterone to normal is beneficial.

Aim. Assessment of safety and effectiveness of injectable long-acting testosterone undecanoate (TU) in hypogonadal men in daily clinical practice.

Methods. An international, multicenter, one-arm, prospective observational study in 23 countries.

Main Outcome Measures. Parameters of erectile function, libido, vigor/vitality, mood, and ability to concentrate assessed by physician interview using items and five-point Likert scales. Physical and circulatory parameters as well as hematocrit, prostate-specific antigen (PSA) levels, glucose control, and lipid profiles.

IPASS. An International, multicenter, Post-Authorisation (after authorized use in respective country) Surveillance Study on long-acting-intramuscular TU conducted at 155 centers in 23 countries in Europe, Asia, Latin America, and Australia. Patients received up to five TU injections during 9–12 months.

Results. Of the 1,493 hypogonadal men enrolled, 1,438 (aged 49.2 ± 13.9 years) having received 6,333 injections were analyzed. Scores of mental and psychosexual functions (libido, vigor, overall mood, and ability to concentrate) improved markedly, while mean waist circumference decreased from 100 to 96 cm. Blood pressure and lipid parameters were altered in a favorable and significant manner. After four TU injection intervals, the percentage of patients with "low" or "very low" levels of sexual desire/libido decreased from 64% at baseline to 10%; moderate, severe, or extremely severe erectile dysfunction decreased from 67% to 19%. At the last observation, 89% of patients were "satisfied" or "very satisfied" with TU therapy. Adverse events and adverse drug reactions (ADRs) occurred in 12% and 6% of patients, respectively, mostly mild to moderate. The most common ADRs were increase in hematocrit, increase in PSA, and injection site pain (all <1%). No case of prostate cancer was observed.

Conclusion. In this largest worldwide sample of hypogonadal men, injectable long-acting TU was effective and well tolerated. **Zitzmann M, Mattern A, Hanisch J, Gooren L, Jones H, and Maggi M. IPASS: A study on the tolerability and effectiveness of injectable testosterone undecanoate for the treatment of male hypogonadism in a worldwide sample of 1,438 men. J Sex Med 2013;10:579–588.**

Key Words. Hypogonadism; Testosterone Undecanoate; Erectile Function; Libido; Mood

Introduction

Hypogonadism is the principal indication for androgen replacement therapy. In androgen replacement therapy, testosterone (T) is administered at doses aiming to reproduce normal endogenous blood T levels in order to achieve physiological exposure of androgen-dependent tissues/organs to T. The better this goal is attained, the better the positive outcomes of androgen replacement in T deficient men may be

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achieved. It will enhance energy, motivation, and endurance and it will produce/restore structural and functional deficits in muscle, bone, erythropoiesis, and glucose/lipid metabolism and psychosexual activity [1], therewith substantially improving quality of life.

T undecanoate (TU) is, in the intramuscularly applied formulation, a relatively new injectable T preparation with a considerably improved pharmacokinetic profile in comparison to other conventional parenteral T esters [2]. After two initial injections with a 6-week interval, the following intervals between two injections are almost always 12 weeks. Plasma T levels with this preparation are almost always in the range of normal men [3,4].

Aim

The present study primarily intends to confirm the so far established safety profile of TU in daily clinical practice during a surveillance period corresponding to four injection intervals in a worldwide and large cohort. Moreover, this observational study is the first ever conducted trial including a large Asian and South American population and will therefore significantly increase the knowledge about TU in different ethnic populations in terms of safety and therapeutic effectiveness. By generally accepted terms, international, multicenter, Post-Authorisation Surveillance Study is a noninterventional study as no intervention in regard to doses or time points was made: the assignment of any patient involved in the study to a particular therapeutic strategy fell within current practice and was not decided in advance by a clinical trial protocol.

Main Outcome Measures

The treatment outcomes were measured by means of the following:

1. Change in laboratory values from baseline to end of observation
2. Change in subjective assessment of the patient from baseline to end of observation
3. Change in intensity of symptoms or disorders associated with low T from baseline to end of observation
4. Assessment of safety parameters (especially regarding the prostate and hematocrit)
5. Patient reported outcome at end of observation

Subjects and Methods

This is an international, multicenter, one-arm, noninterventional (see above for definition), prospective observational Post-Authorisation Surveillance Study on long-acting-intramuscular TU conducted at 155 centers in 23 countries in Europe, Asia, Latin America, and Australia. The objectives of the study were the following: (i) to assess treatment outcomes of male hypogonadal patients receiving TU under real-life conditions; (ii) to assess the treatment continuation rate in patients treated with TU after four injection intervals; and (iii) to confirm the so far established safety profile of TU as published in pertinent studies [3,5]. This is a prospective case-controlled noninterventional registry study. This type of study has methodological limitations but represents an additional source of information from a "real-life setting" in comparison to the established placebo-controlled intervention trials. Patients suffering from primary or secondary hypogonadism or late onset hypogonadism (LOH), eligible for T treatment, were recruited. The study included both men who have had earlier other forms of T administration and newly diagnosed, not yet treated cases of hypogonadism. The definition of secondary hypogonadism requires the presence of pathologies of the hypothalamus/pituitary, while LOH is a mixed form of hypogonadism with deficiencies of both Leydig cells and impairments of central regulatory mechanisms stimulating T secretion, mostly due to metabolic disturbances [6].

Every patient was diagnosed with hypogonadism in agreement with internationally accepted standards, requiring the presence of both signs and symptoms of androgen deficiency and low serum levels of total T. Cut-off levels for total T were at the discretion of the investigator and country specific, but ranging between 8 and 12 nmol/L for newly diagnosed, treatment-naïve patients according to the published references [7], widely adopted by scientific societies. Another recommendation followed was to use the limits of the own reference laboratory as recommended by the American Endocrine Society [8]. Levels of free T were not considered a universal tool for the diagnosis of hypogonadism in this study, as various countries handle this topic differently.

For patients already on substitution therapy, a wash-out period was regarded as not necessary, but hypogonadism according to the above-mentioned guidelines had to be established in every patient's history.

Symptoms of androgen deficiency were assessed based on parameters of erectile function, libido, vigor/vitality, mood, and ability to concentrate by the physician's interview using items and five-point Likert scales originating from validated tools: the Aging Male Symptoms (AMS) scale [9] and the International Index of Erectile Function-5 (IIEF-5) [10] (see below).

Subjects received up to five TU injections during an observation period of typically 9–12 months. Between the first and second injections of TU, there was an interval of 6–10 weeks, and subsequent injections were given with an interval of 12 ± 2 weeks [3]. To ensure a standard treatment regimen in all participating countries, a so-called Summary of Product Characteristics was followed (this is a mandatory part of the legal authorization process describing how to use the drug safely and effectively). The indication for T administration was decided by the treating physician who also assessed potential contraindications against T treatment such as prostate pathology and/or an elevated hematocrit.

Patients with contraindications to T replacement therapy were excluded from the study. Exclusion criteria were the established contraindications, androgen-dependent carcinoma of the prostate or of the male mammary gland, past or present liver tumors, hypersensitivity to the active substance or to any of the excipients, and desired paternity. There were minor specifics in some countries, such as Korea, which lists additional contraindications (severe hepatic impairment, severe cardiac failure and renal failure, and prostatic hyperplasia).

Blood pressure, heart rate, weight, and waist circumference were recorded at each visit, and height was documented at the inclusion visit.

Waist circumference has been reported to be inversely associated with total and free T [11,12] and is a practicable indicator of intra-abdominal fat mass [13].

The laboratory measurements at each time point of injection include the following: total T, estradiol, sex hormone binding globulin, follicle stimulating hormone, luteinizing hormone, and prostate-specific antigen (PSA). The laboratory measurements at the discretion of the local investigators include the following: hemoglobin A1C (HbA1c), serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Subjective assessment by the patient regarding parameters of erectile function, libido, vigor/vitality, mood, and ability to concentrate was assessed by physician interview using items and five-point Likert scales originating from validated tools: the AMS scale [9] and the IIEF-5 [10]. To this end, standardized interviews with predetermined questions were used as validated translations are not available in the language of every participating country. It was, hence, assumed that the possibility of error or bias was largely reduced when the physician followed a guided interview instead of using questionnaires handed out to patients. Admittedly, the subjective question tools were not validated and this might produce a possible source of "statistical noise."

Also other symptoms associated with low T levels, such as hot flushes, excessive sweating, sleep disturbances, and decreased physical strength, were assessed at each visit based on five-point rating scales.

At the end of the observational period, the patient made a subjective rating on his treatment satisfaction, the overall tolerability, and, if applicable, the effectiveness of the treatment compared with the previous form of androgen therapy.

For safety, digital rectal examination (DRE) was documented at every visit, as well as laboratory measurement of PSA and hemoglobin and hematocrit.

The nature of the observational study was explained to all participants. If requested by local regulations, the patients signed the informed consent form after having received information about the study by the physician before participating in the study.

Statistical Analysis

Statistical analyses are descriptive but also include overall chi-square tests for relative data (percentage values) and analysis of variance (ANOVA) analyses for continuous variables, such as waist circumference. Analyses were performed pooled for all countries. Quantitative parameters were described by absolute and relative frequencies, and metric parameters were described by arithmetic mean and standard deviation: (i) patient demographic data (age and ethnic group); (ii) medical history (classification of hypogonadism and previous androgen therapy); (iii) drug treatment (TU continuation rate); (iv) vital signs and anthropometric measurements (blood pressure, heart rate, height, weight, and waist circumference) and change in vital signs/anthropometric measurements from baseline to end of observation; (v) DRE; (vi) laboratory values and change in labora-

tory values from baseline to end of observation; (vii) symptoms or disorders associated with low T (hot flushes or excessive sweating, sleep disturbances, decreased physical strength, and erectile dysfunction [ED]) and change in symptoms or disorders from baseline to end of observation; (viii) subjective assessment of the patient (libido, vigor/vitality, mood, and ability to concentrate) and change in subjective assessment from baseline to end of observation; (ix) adverse drug reactions; and (x) final outcome assessment by the patient (treatment satisfaction, overall tolerability, and effectiveness of the treatment compared with the previous form of androgen therapy if applicable).

Data for those patients not completing the trial were analyzed as last visit documented (LVD) (using the methodology "last observation carried forward"). Thus, every subject's data were included in the analysis, not only those of men completing the trial.

Results

In total, 1,493 patients were enrolled in 23 countries worldwide. Caucasians were the majority (72.5%), followed by Asians (19.7%), others, mainly Latin American men (7.5%), and Afro-Carribeans (0.3%). Data were complete for evaluation in 1,438 men at baseline and 1,140 men at the time of injection 5.

The premature discontinuation rate was 17.5%, of which less than a quarter were due to discomfort at injection sites and the majority were due to other reasons unrelated to adverse drug reaction. Missing information for evaluation was present in 63 men. The main reason was "patient lost to follow-up" and "withdrawal of consent" (N = 136). Overall, adverse drug reactions of various kinds (none with N > 4) led to discontinuation in 31 men (mostly a degree of discomfort with the injection, see also below). Evidently, this has to be considered as a potential source of bias.

Therefore, not only the patients completing the study including visit 5 were analyzed but also the LVD (in terms of last observation carried forward). The data of LVD were practically identical to those of visit 5 and do not provide additional information; the statistical results detailed in the article are completely supported and corroborated by the comparison of baseline data to the data of LVD.

Description of Cohort

Baseline parameters were as follows: age (49.2 ± 13.9 years); body weight (86.8 ± 17.6 kg); and waist circumference (99.5 ± 15.25 cm). Previous androgen therapy, N = 641 (54%), consists of injections of T esters (37.4%), T gels (44.9%), and T capsules (17.5%). The serum T was 9.6 ± 7.5 nmol/L. The comorbidities were as follows: diabetes mellitus (14.0%), hypertension (26.1%), dyslipidemia (22.2%), and ED (64.7%).

Age stratification was as follows: >75 years: 20 (1.4%); 65–74 years: 178 (12.4%); 55–64 years: 365 (25.4%); 45–54 years: 386 (26.8%); 35–44 years: 239 (16.6%); and <35 years: 243 (16.9%).

Serum T Concentrations

Mean trough serum total T levels before starting TU administration were 9.6 ± 7.5 nmol/L. Total T levels presented here reflect the summary of both treatment-naïve and already treated patients (the latter had no washout, see above). Patients naïve to treatment had to be diagnosed with low total T according to the guidelines (median total T was 8.3 nmol/L [0.1–11.4 nmol/L]). The overall free T was 314 ± 214 pmol/L. Before injection 2, these were 15.2 ± 8.5 nmol/L and 546 ± 260 pmol/L; before injection 3, these were 16.0 ± 7.3 nmol/L and 578 ± 211 pmol/L; before injection 4, these were 17.0 ± 7.4 nmol/L and 624 ± 279 pmol/L; and before injection 5, these were 17.3 ± 7.3 nmol/L and 634 ± 302 pmol/L (ANOVA for both $P < 0.0001$).

Subjective Assessment of Hypogonadism-Related Symptom Intensity

There was a significant improvement of the overall levels of sexual desire/libido: a very low/low level at baseline decreased from 64% of patients to 13% after two injections and to 10% at the time of injection 5. A high/very high level of libido increased from 10% of patients at baseline to 42% after two injections to 61% at the time of injection 5 (overall chi-square test: $P < 0.0001$).

The results below indicate that the proportions of patients who reported low levels of the well-being parameters declined during T therapy. Improvements in the overall level of vigor/vitality are presented in Figure 1, showing significant improvements over each injection interval (overall chi-square test: $P < 0.0001$). With regard to mood (Figure 2) and overall ability to concentrate, similar patterns were encountered (Figure 3) (overall chi-square test: $P < 0.0001$). When patients who have had previous T treatment were compared with patients without previous T treatment, in both groups the ability to concentrate increased (chi-square tests: $P < 0.0001$).

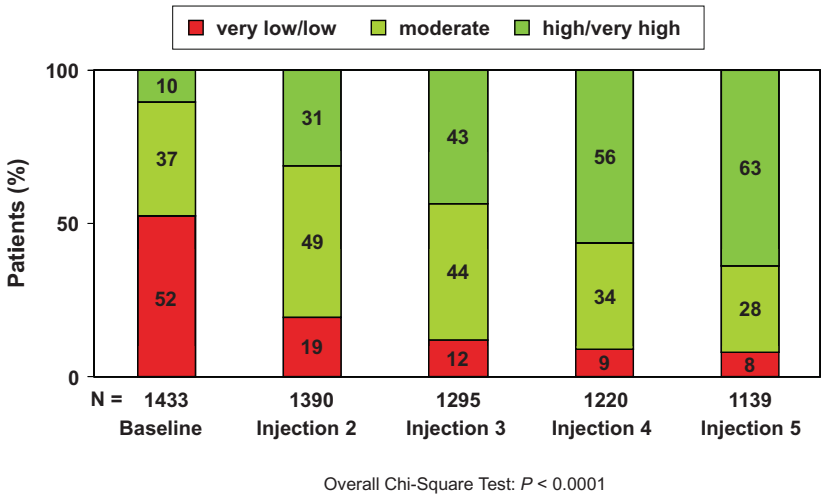

Figure 1 Changes in the subjective overall assessment of vigor. The stacked bars indicate the respective distribution at each time point during the course of the trial. The patterns were analyzed by overall chi-square tests for significance. Data for those patients not completing the trial were analyzed as last visit documented (in terms of last observation carried forward). These data are practically similar to visit 5 and yield the same statistical results.

Hot flushes improved: no hot flushes were encountered in 49.8% at baseline and in 79.1% at the time of injection 5. Moderate hot flushes declined from 17.5% at baseline to 4% at the time of injection 5 and severe from 7.6% at baseline to 0.5% at the time of injection 5. Complaints of excessive sweating showed a similar pattern of improvement.

At baseline, 65% of patients reported moderate, severe, or extremely severe ED, decreasing to 19% after TU therapy at the time of injection 5 (overall chi-square test: $P < 0.0001$). Approximately 56% of patients with some degree of ED, who did not receive concomitant phosphodiesterase type 5 (PDE5) inhibitor therapy, reported a decrease in severity of ED following TU therapy.

When patients who had had previous T treatment were compared with patients without previous T treatment, in both groups the severity of ED decreased (chi-square tests: $P < 0.0001$) (data not shown). Over the observation period, there was a concomitant use of PDE5 inhibitors in 15–16% of the patients, and while receiving TU there was an improved response to PDE5 inhibitor therapy from 35% at baseline to 57% at the time of injection 5 (overall chi-square test: $P < 0.0001$). The proportion of patients who reported no or a low response to PDE5 inhibitor therapy declined from 25.2% at baseline to 12.2% at the time of injection 5 (Table 1). The proportion of patients who reported a sufficient response to PDE5 inhibitor therapy (high and very high response) increased from 35.1% at baseline to 56.6% at the final visit/injection 5 (Table 1). Overall, 26.1% of the patients receiving a PDE5 inhibitor experienced an improvement in the response to their ED treat-

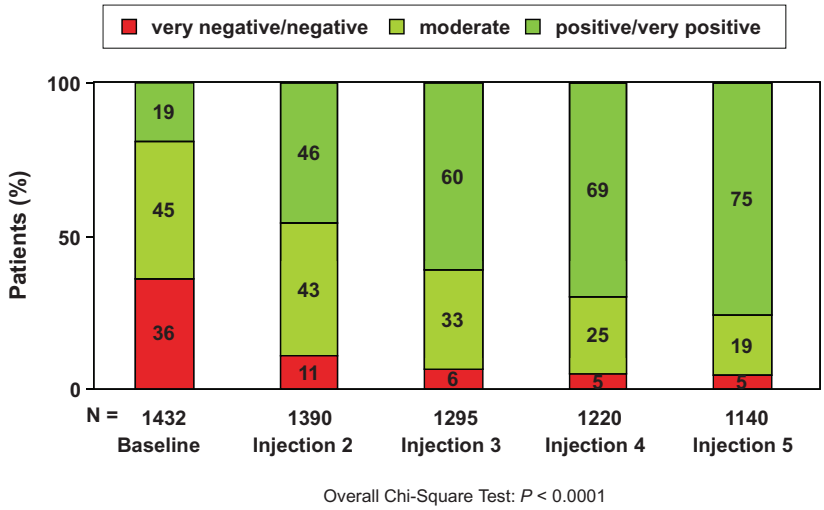

Figure 2 Changes in the subjective overall assessment of general mood. The stacked bars indicate the respective distribution at each time point during the course of the trial. The patterns were analyzed by overall chi-square tests for significance. Data for those patients not completing the trial were analyzed as last visit documented (in terms of last observation carried forward). These data are practically similar to visit 5 and yield the same statistical results.

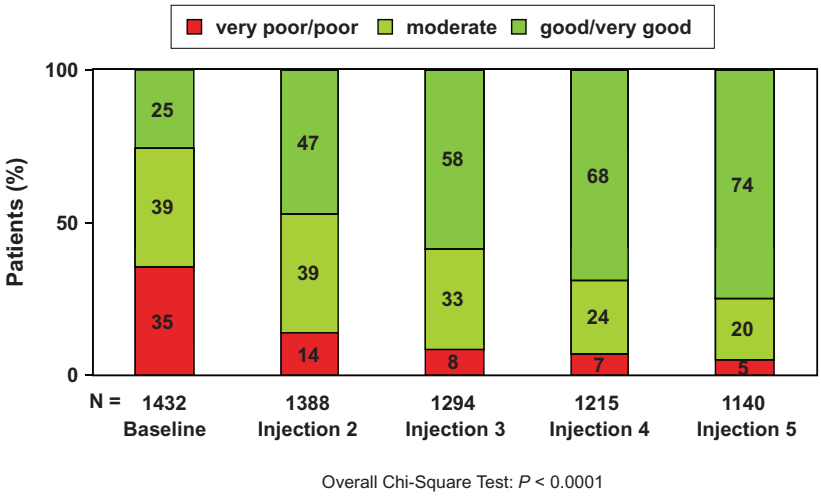

Figure 3 Changes in the subjective overall assessment of the ability to concentrate. The stacked bars indicate the respective distribution at each time point during the course of the trial. The patterns were analyzed by overall chi-square tests for significance. Data for those patients not completing the trial were analyzed as last visit documented (in terms of last observation carried forward). These data are practically similar to visit 5 and yield the same statistical results.

ment (Table 1), which was highly statistically significant (overall chi-square test $P < 0.0001$).

During the course of TU treatment, there was an improved sleep quality from 56% at baseline to 88% at the time of injection 5 (overall chi-square test: $P < 0.0001$).

Satisfaction as assessed by the patients themselves was as follows: very satisfied (35.4%); satisfied (35.4%); minimally satisfied (5.0%); neither satisfied nor dissatisfied (2.2%); minimally dissatisfied (0.5%); dissatisfied (0.7%); and very dissatisfied (0.2%).

Subjective effectiveness compared with previous androgen therapy as assessed by the patient was as follows: much better (50.5%); (somewhat) better (33.4%); same (7.3%); (somewhat) worse (2.4%); and much worse (0.4%).

Objective Metabolic Parameters

Blood pressure and serum lipid profiles changed during treatment in a favorable and significant manner (Table 2).

The subgroup of patients whose baseline level of HbA1c was elevated (>6.1%) (mean 7.9%, N = 60), thus fulfilling the International Diabetes Federation criteria for the diagnosis of impaired glucose metabolism/type 2 diabetes mellitus [14], showed a decline of—1.1%—points within the whole treatment period (*t*-test: $P < 0.0001$).

Table 1 Response to phosphodiesterase type 5 inhibitors (none/low/moderate/high/very high) at baseline, visit 2, visit 3, visit 4, and visit 5 during treatment with parenteral testosterone undecanoate

	None	Low	Moderate	High	Very high
Baseline	12 (5.41%)	44 (19.82%)	85 (38.29%)	64 (28.83%)	14 (6.31%)
Visit 2	4 (1.86%)	19 (8.84%)	83 (38.6%)	92 (42.79%)	15 (6.98%)
Visit 3	2 (0.99%)	16 (7.88%)	70 (34.48%)	86 (42.36%)	25 (12.32%)
Visit 4	4 (2.01%)	14 (7.04%)	57 (28.64%)	88 (44.22%)	27 (13.57%)
Visit 5	7 (3.7%)	16 (8.47%)	59 (31.22%)	79 (41.8%)	28 (14.81%)

Overall chi-square test: $P < 0.0001$

Table 2 Change of metabolic parameters over five injection intervals of parenteral testosterone undecanoate

Parameter	Unit	Baseline: mean ± SD	Injection 5: mean ± SD	*P* (*t*-test)
Blood pressure (systolic)	mm Hg	129.3 ± 14.6	127.2 ± 13.1	0.0002
Blood pressure (diastolic)	mm Hg	79.8 ± 9.8	78.7 ± 8.9	0.016
Serum triglycerides	mg/dL	160.0 ± 100.5	143.9 ± 87.2	<0.0001
Serum total cholesterol	mg/dL	197.0 ± 46.5	187.3 ± 44.3	<0.0001
Serum HDL cholesterol	mg/dL	47.4 ± 18.3	48.3 ± 16.1	0.3
Serum LDL cholesterol	mg/dL	115.9 ± 40.6	110.9 ± 39.2	0.0017

HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation

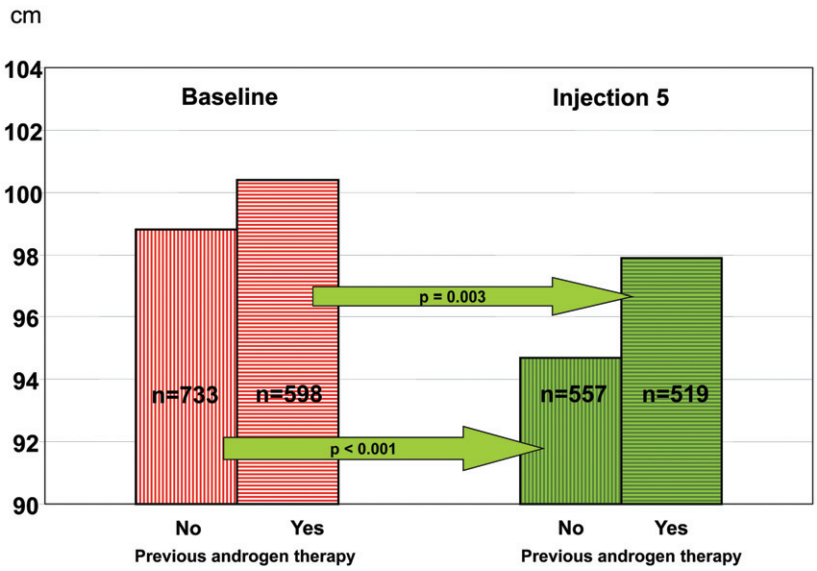

Figure 4 Changes in waist circumference in patients pretreated with testosterone and those naïve to substitution treatment. Data for those patients not completing the trial were analyzed as last visit documented (in terms of last observation carried forward). These data are practically similar to visit 5 and yield the same statistical results.

There was a slight decrease of body weight, not reaching statistical significance ($P = 0.08$), but the decrease in waist circumference measured at baseline and at the time of injection 5 (for no previous T treatment and for pretreated patients) was statistically significant (ANOVA: $P < 0.0001$ and $P = 0.003$, respectively, see Figure 4).

Safety Aspects

Adverse drug reactions considered related to TU therapy by the investigators were relatively rare: N = 83 (5.8%). Only in one case there was a serious adverse reaction: prostate enlargement and urinary retention (0.1%). Most common adverse drug reactions were an increase of the hematocrit, an increase of the PSA, and pain at the injection site, all occurring in <1%. Overall, adverse drug reactions of various kinds (mostly forms of discomfort with the injection, none N > 4) led to discontinuation in 31 men. Overall mean PSA levels increased from 1.1 ± 0.9 to 1.3 ± 1.2 ng/mL and remained stable afterwards ($P < 0.0001$).

Table 3 presents data on the course of values of PSA, stratified to pretreatment with T or no pretreatment. PSA exceeded 4 ng/mL in 11 men. There were clinical reasons to perform a prostate biopsy in four cases, but in no case prostate cancer was observed. Following the guideline of the American Endocrine Society, PSA velocity is a valid tool in the diagnosis of prostate cancer, but it is less indicative during the first year of substitution treatment with T when PSA rises upon restoring the hypogonadal status of the patients. PSA velocity should be used only if there are longitudinal PSA data for more than 2 years and with the reference value taken at month 6 of treatment [8].

Hematocrit rose gradually from 42.8 ± 6.6% at baseline to 44.5 ± 6.1% at the time of injection 5 ($P < 0.0001$). A rise in hematocrit within the normal range cannot be seen as adverse event per se. The 75% quartile was 46.4% for baseline and 48.8% for injection time point 5.

Adverse cardiac events were reported in seven patients. These were atrial fibrillation (N = 2), myocardial infarction (N = 2), bradycardia (N = 1), palpitations (N = 1), and not further described cardiovascular disorder (N = 1). No cases of heart failure and no edema associated with heart failure

Table 3 PSA (ng/mL) at sample 1, sample 2, sample 3, sample 4, and sample 5 during treatment with parenteral testosterone undecanoate

	Mean	SD	Min	Q1	Median	Q3	Max
(a) No previous androgen therapy							
Baseline	1.1	0.95	0.0	0.5	0.9	1.5	6.7
Visit 2	1.3	1.08	0.1	0.6	1.0	1.6	7.7
Visit 3	1.4	1.17	0.1	0.6	1.0	1.8	7.5
Visit 4	1.3	1.09	0.1	0.6	1.0	1.8	8.5
Visit 5	1.2	1.04	0.1	0.4	0.8	1.5	5.8
(b) With previous androgen therapy							
Baseline	1.0	0.92	0.0	0.4	0.7	1.2	5.5
Visit 2	1.1	1.07	0.0	0.5	0.8	1.3	6.7
Visit 3	1.2	1.17	0.1	0.5	0.9	1.4	8.9
Visit 4	1.1	0.99	0.1	0.5	0.8	1.3	7.5
Visit 5	1.1	1.02	0.3	0.6	0.8	1.2	10.1

Only cases with any information from the respective sample are included in this table.
PSA = prostate-specific antigen; SD = standard deviation; Min/Max = minimum/maximum; Q1: 25% quartile; Q3: 75% quartile

were reported. These events were seen in men with preexisting cardiovascular impairment; no de novo incidents were recorded.

Discussion

This ambitious project assessed the effects of long-term T therapy for hypogonadism in men from different parts of the world, i.e., Europe, Asia, Latin America, and Australia. This was performed in a setting with multiple centers and multiple laboratories that might affect statistical rigor, but its outcome reflects a "real world situation" especially in regard to the various participating centers, laboratories, and ethnicities. The setting is very likely to create statistical noise rather than outright bias, but they both could not be excluded, as there was no randomization or placebo group.

This study of injectable long-acting TU in the largest worldwide sample of hypogonadal men documents that this form of therapy is effective and well tolerated in daily clinical practice in a worldwide setting. Clinically relevant efficacy could be documented especially regarding sexual function.

Figures 1–3 show a continued improvement in a number of parameters over time, confirming earlier observations that benefits from T therapy are immediate but take time to unfold to a full extent. Figure 4 also shows that improvements were observed in non-T-naïve patients, maybe on the basis of higher serum T levels or longer duration of T exposure [15]. Data for those patients not completing the trial were analyzed as LVD (in terms of last observation carried forward). In men completing five visits, data at visit 4 were practically similar to those collected at visit 5 and yield the same statistical results.

When TU was used as monotherapy for treatment of ED, a significant improvement was observed. In men who had earlier been treated with other T preparations, a further improvement was noted when these patients had switched to treatment with TU. When PDE5 inhibitor medication was used, TU further improved therapeutic success.

There was no significant weight loss but waist circumference decreased significantly upon treatment with TU. Significant favorable changes in lipid profiles were observed in serum triglyceride, total cholesterol, and LDL cholesterol. There are some reports that HDL-cholesterol levels decrease upon administration of T, however mainly in studies with higher mean T values at baseline [16]. This was not the case in this study; HDL-cholesterol levels remained stable during treatment. HbA1c levels improved significantly when previously elevated; elevated HbA1c levels indicate an unfavorable or abnormal glucose metabolism/insulin resistance. This is consistent with a recent meta-analysis [4] and indicates a favorable effect of TU on abnormal glucose metabolism/insulin resistance.

One effect not particularly addressed in earlier reports is the positive effect of T therapy on sleep efficiency. As oxygen desaturation during sleep is a known problem in obese people [17], it might be speculated that the observed effect is related to the reduction of abdominal fat mass, as indicated by the loss of waist circumference. It has also been hypothesized whether restoration of T levels has a direct effect on cerebral sleep mechanisms.

Excessive sweating or hot flushes have earlier been described in hypogonadism, but not to the extent as in this article and in its positive reaction to T therapy [18–20]. This disturbing symptom should gain, as well as sleep disturbances, more attention in the diagnosis and treatment of hypogonadal men.

TU was a well-tolerated treatment in patients with male hypogonadism. The great majority of patients rated the tolerability as "very good" or "good." At the final observation, 89% of patients were "satisfied" or "very satisfied" with TU therapy. There was a low incidence rate of adverse drug reactions and a low rate of discontinuation (Table 2). Adverse drug reactions that occurred during therapy were consistent with the established safety profile of TU. No serious or hitherto unknown adverse drug reactions were reported.

Overall, TU demonstrated to be a safe treatment option for male hypogonadism. Abnormal increases in hematocrit and PSA were rarely observed. There was one case of serious prostatic hyperplasia and urinary retention.

Under close surveillance, no case of prostate cancer was detected. We a priori expected to encounter patients with prostate cancer in this large study, but this was not the case. The overall safety of T treatment is indicated by this and also by the safety pattern of surrogate markers such as changes in PSA and hematocrit. As shown in Table 3, there were no significant differences between the group (a) having been treated with T previously and (b) being T-naïve patients. This seems to demonstrate that exogenous T does not exert major effects on the prostate, at least in the short term of this study, though performed in a wide population.

The overall incidence of cardiovascular problems (N = 7), with two myocardial infarctions (age of subjects: 60 and 76 years, no increased hematocrit observed), attests to the safety of the regimen. The result corroborates previous data on cardiovascular safety of TU and also of other T preparations, for instance, in men with stable chronic heart failure and with median age of 70 years [21]. This is consistent with the results of a recent placebo-controlled study of 262 frail and prefrail men, mean age 73.8 years, receiving T gel for 6 months where one case of prostate cancer was encountered in the placebo group [22] and in a study of 131 men, mean age 77.1 years (range 57–95), receiving T gel for up to 24 months where 10 deaths occurred (three in T group and seven in placebo, not significant [NS]) [23]. These results document that proper monitoring, as well as management of the dose of medication, is mandatory. The adverse results concerning cardiovascular health in a recent study might be related to overdosing T gel in frail men [24].

Summarizing, this multicenter approach with a pattern of "daily practice use" of TU in its injectable form left more space for individual titration and patient adaptation than in a more tightly regulated study protocol and was able to demonstrate the favorable effects of T substitution in men with documented hypogonadism. These beneficial effects of therapy have been previously described in smaller settings. Using a method providing both stable serum concentrations of T and a high grade of compliance due to the three-monthly injections performed by the physician, this study corroborates and strengthens the modern view on the desirability and efficacy of substitution therapy in men with proven hypogonadism, also in a "real-life" setting. The use of the long-acting injectable TU allows an appropriate guidance of the patient embarking on a new treatment. The extensive experience from this study in "everyday clinicians' " offices provides important insights, experience, and important knowledge to physicians who offer T treatment to their patients.

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